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(54) Total synthesis method for making an indole structure derivative product class, of the triptamine type, in particular, melatonin or N-acetyl-5-methoxytriptamine type, having a high purity degree and easily soluble, for therapeutic use against acquired immuno-deficiency syndromes

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Description

The present invention relates to a total synthesis method for preparing an indole structure derivative product class,of the tryptamine type,in particular melatonin or N-acetyl-5-methoxytryptamine,having a high purity degree and easily soluble,for therapeutic use against acquired immuno-deficiency syndromes.

As is known,it has been found that melatonin (MTL),administered with suitable doses and at given times,is able of reducing hypothalamic protein synthesis and hypophisis and that it,moreover,may inhibit the synthesis of gonadotrophins.

Such an action is probably exerted by means of a modulation of gene transcription,as well as on the secretion of the GH and PRL, growth factors under particular conditions.

The above mentioned overall effects,which are associated with other particular actions,as disclosed in a more detailed way hereinafter,justify as useful,even if not indispensable,the use of melatonin against tumours.

In fact one may reasonably think that melatonin pertains to that class of drugs able of interfering with the growth of neoplastic cells.

On the other hand,also known is the fact that presently available methods for making the tryptamine structure having the hydrogen atom at the 5-position replaced by the group OCH_3,are based on a series of chemical reactions providing 2-carboxyethyl-3-(2-phthalimidoethyl)-5-methoxy-indole, from which is obtained 5-methoxytryptamine by means of a number of comparatively complex and low-yield processing steps.

More specifically,known prior art methods comprise an alkaline saponifying step providing 2-carboxy-3-(2-O-carborybenzamidoethyl)-5-methoxy-indole acid wich is then dry decarboxilated at 250 °C in order to form phthalimidoethyl-5-methoxy-indole,which is then water hydrazinolized to provide 5-methoxytryptamine.

The process described in Chem Abstr., 82, no. 21, 1975 differes in that after hydrolysis, decarboxylation, and hydrazinolysis of the indolecarboxylate to give the triptamines III, no further purification process has been carried out.

In order to obtain pure N-acetyl-5-methoxytryptamine or melatonin with a high yield,it is necessary to have a high purity starting product,that is 5-methoxytryptamine.

Known conventional purifying methods,based on the use of solvents or mixtures thereof,on the other hand, have not been able of providing a sufficiently high purity degree with a contemporaneous high production yield.

SUMMARY OF THE INVENTION

Accordingly,the main object of the present invention is to overcome the above mentioned drawback by providing a method for making,with high production yields,very pure 5-methoxytryptamine,which method essentially comprises a synthesis known per se with respect to the reagents,but carried out by new techniques starting from 2-carboxyethyl-3-(2-phthalimidoethyl)-5-methoxy-indole.

Another object of the present invention is to provide such a method which,in addition to simplifying the processing steps,is able of making melatonin starting both from 5-methoxytryptamine,in raw form, and from pure 5-methoxytryptamine.

Yet another object of the present invention is to provide a total synthesis method which affords the possibility of obtaining a very pure and reliable products,with consistent curative properties.

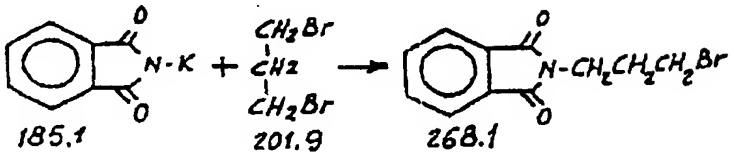
According to one aspect of the present invention, the above mentioned objects,as well as yet other objects, which will become more apparent hereinafter,are achieved by a total synthesis method for making an indole structure derivative product class,of the triptamine type,in particular melatonin or N-acetyl-5-methoxytryptamine ,having a high purity degree and easily water soluble for therapeutic use against acquired immuno-deficiency syndromes comprising the steps of combining potassium phthalimide and dibromopropane,to provide 3-bromopropylphthalimide,adding acetacetic ester in the presence of anhydrous ethanol dissolved sodium to provide ethyl-2-acetyl-phthalimido-pentanoate,adding diazo-p-anisidine to provide 2-carboxyethyl-3-(2-phtali-midoethyl)-5-methoxy-indole,which is processed,in a first step,by NaOH 2N up to a complete solution and,then,by H_2SO_4 (at 20%) to provide raw 5-methoxytryptamine,whichis purified by means of hexamethyldisilazane,so as to provide the related mono- and bi-derivative therefrom, by means of an aqueous methanol hydrolysis,there is obtained the starting compound.

BRIEF DESCRIPTION OF THE DRAWING

Further characteristics and advantages of the present invention will become more apparent from the following detailed description of the total synthesis method according to the invention,with reference to the

chemical diagram shown in the accompanying drawing table.

DESCRIPTION OF THE PREFERRED EMBODIMENT



The method according to the invention comprises the step of preparing 3-bromopropylphthalimide as follows:

into a 3-neck 1-litre flask,provided with stirrer and cooling medium,there are introduced 101 g (0.5 moles) of 1.3- dibromo-propane,250 ml acetone and 15g K-phthalimide,by reflowing the mixture under stirring.At 1 hour time intervals there are added further (15 + 10 + 6.3) g K- phthalimide(46.3 g corresponding to 0.25 moles),by holding under reflux for a total period of 24 hours.

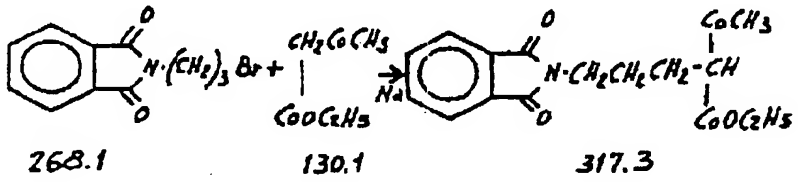
At the end of this period the precipitated KBr is filtered and acetone is evaporated in a rotating evaporating device;the obtained oil is distilled under vacuum(as provided by a water pump) and there are recovered 48.5g(0.25 moles) of 1,3 - dibromopropane,which is distilled at 69-70 • C.The residue (dissolved before solidification in the distillation flask) is crystallized twice from ethanol,so as to remove the small amount of formed diphthalimidopropane.

There are thus obtained 48.2 g,melting point 72 • C (Tottoli),with a yield of 72%.

Purity is controlled by TLC on silica gel, using as eluent benzene-acetone (45 :5),freshly prepared,Rf of about 0.95 (diphthalimidopropane having a lower Rf).

By analogous reactions,in which K-phthalimide is added once,there is obtained a product which contains greater amounts of diphthalimidopropane,thereby it is necessary to purify by distillation (e.g. 150 • C/0.25mm) by using a Vigreux device without cooling,since the distillate tends toward solidification.The yield is substantially equal to the above disclosed yield.

Preparing of ethyl-2-acetyl-5-phthalimido-pentanoate



In a three-neck flask having a capacity of 500ml, provided with $CaCl_2$ cooling system and stirrer there are dissolved 4.60 g (0.2 g/A) Na in 100 ml anhydrous ethanol.To the solution, at room temperature,there are added 27.32 (0.21 moles) of acetacetic ester and then,after ten minutes,40 g of 3- bromopropylphthalimide and,after one hour,further 12.5 g (in total 52.5g corresponding to 0.196 moles),by holding the reflux processing and continuing for further three hours.

At the end of this period,sodium bromide is filtered,the solution is neutralized by 2N HCl and ethanol is evaporated under reduced pressure.The residue is recovered with ether,washed by H_2O x 2,dried on anhydrous Na_2SO_4 and the solvent is evaporated,thereby providing a light yellow oil which is crystalized by dissolving it in a minimum ethanol amount by adding a small amount of ether, leaving it overnight in a refrigerator.

There are thus obtained 45g (yield 72%) of white crystalline solid,with m.p 60 • C (Tottoli).Upon recrystalisation there is obtained a m.p of 63 • C.Product also cristalizes from benzene-petroleum ether.

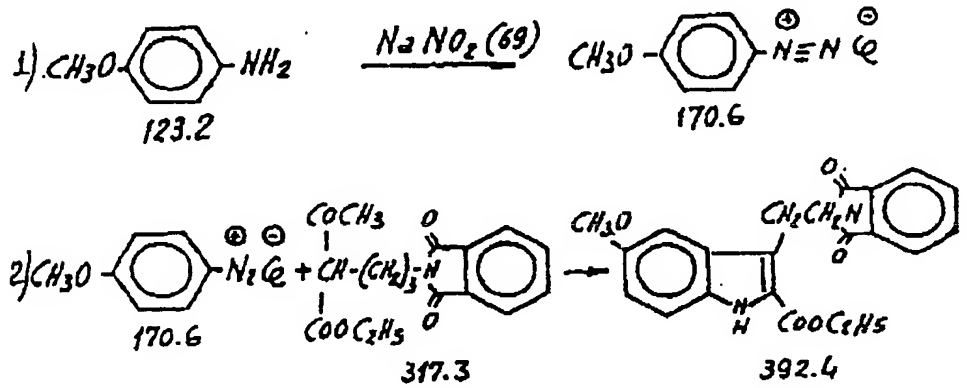
TLC on silica gel,benzene-acetone (45:5),Rf about 0.70.

Purification of 4-anisidine

A sample of 4-anisidine,of a very dark colour, is dissolved in an excess of 2N HCl and the solution is repeatedly extracted with chloroform as far as the colour is no longer extracted.

The acid solution is boiled with decolorizing charcoal and filtered hot.The strongly cooled filtrate is alkalized with concentrated NaOH and extracted with chloroform.The chloroform solution is dried on anhydrous Na_2SO_4 and evaporated under reduced pressure.The residue is crystalized from benzene thereby providing a white lamellae product with a melting point of 57 • C (Tottoli).

Preparing of 2- carboxyethyl-5-(2- phthalimidoethyl)-5-methoxy-indole



24.64 g (0.2 moles) p-anisidine in 80ml ethanol, 120 ml water and 80 ml (0.96 moles) 37% HCl are diazotized at 0-5 • C with 14.5 g (0.21 moles) $NaNO_2$ in 40 ml water;at the end the reaction is continued for other 30 minutes at the same temperature.

The thus obtained diazonium salt solution is added to a solution (stirred and held at 0 • C) of 63.46g (0.2 moles) of ethyl-2-acetyl-5-phthalimido-pentanoate and of 130.64 g (0.96 moles) of sodium acetate trihydrated in 700 ml ethanol.The reaction is continued for 1 hour (the end pH must be inculded in the 5-6 range)-;then the solution is brought to room temperature under stirring for other three hours.

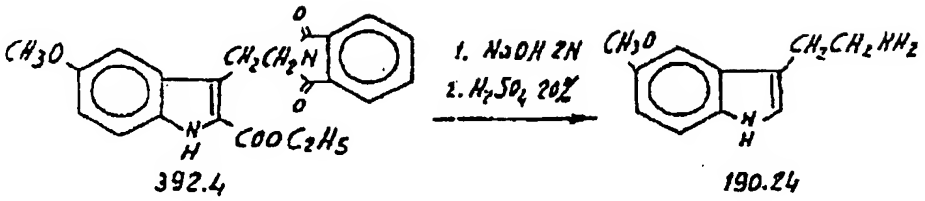
At the end of this period,the mixture is diluted with 2 l water and extracted with CH_2Cl_2 three times;the organic phase,after washing with water and drying on anhydrous Na_2SO_4,is evaporated,thereby providing 89.2 g of a dark red oil which is dissolved in a minimum amount of ethanol and introduced into a 3-neck 1 litre capacity flask,provided with stirrer,cooler and loading funnel.By stirring and heating there are added in 20 minutes 480 ml of a 10% solution of steaming HCl in ethanol,and then, refluxing for 2 hours.

At the end of this period,the mixture is cooled down (for a night in a refrigerator or for 3 hours on an ice bath) and filtered by fully washing with methanol,water and methanol again.The dry solid material has a weight of 57.3 g (yield 73%),with a m.p of 234-7 • C (Tottoli).

By recrystalisation from glacial acetic acid there are obtained 54.9g (yield 70%) with m.p 239-40 • C (Tottoli).

TLC on silica gel,concentrated benzene-methanol-ammonia (50:10:1),Rf about 0.90.

Preparing of 5-methoxytriptamine



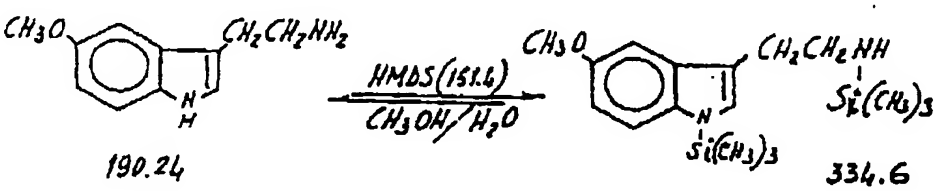
Into a 3-neck 3 litres flask,provided with stirrer, cooler and loading funnel,there are introduced 58.86g (0.15 moles) of 2-carboxyethyl-3-2-phthalimidoethyl-5-methoxy-indole and 187.5 ml (15g;0.375 moles) of 2N NaOH and the mixture is refluxed at 135 • C for 2.5 hours, thereby providing a complete solution.

Holding constant stirring and temperature,there are added,in 30 minutes,750 ml of H_2SO_4 (at 20%) (v/v), further refluxing for 4 hours.

At the end,the solution is cooled (for a night in a refrigerator or for 3 hours in an ice bath),by removing by filtration the precipitated phtalic acid.The solution is alkalysed with 30% NaOH, constantly cooled and extracted by CH_2Cl_2 x 3;the collected extracted materials are washed with water,dried on anhydrous Na_2SO_4 and evaporated,thereby providing 20.25g (yield 71%) of raw 5-methoxytryptamine.

TLC on silica gel,sat.$CHCl_3$,NH_4OH-methanol (50:2),Rf about 0.65.

Purifying of 5-methoxytryptamine



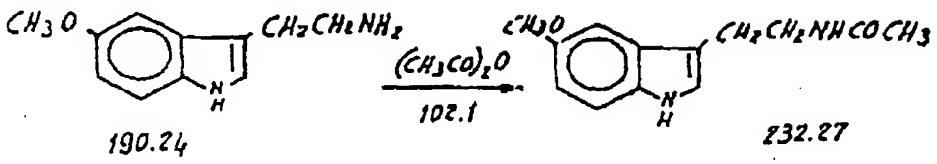
To purify 5-methoxytryptamine,19g (0.1 moles) of 5-methoxytryptamine (raw) and 76 ml (58.86-0.36 moles) of hexamethyldisilazane (HMDS) are refluxed for a night in a flask with sodium hydroxide protected cooling.

The solution is first distilled under normal pressure for recovering excess HMDS (43.6 g;0.27 moles; m.p 124-5 • C) and then under a reduced pressure,thereby providing a mixture of biderivative (20.26g;b.p. 135-40 • C at 0.1 Torr) and monoderivative material (5.25g;b.p.165 • C at 0.1 Torr).

The silyl derivative is hydrolized with aqueous methanol,thereby providing 15.36g (0.08 moles) with a yield of 80%.The mixture is crystalized from ethanol,so as to provide a white product having a m.p of 120-1 • C (Tottoli).

Preparing of N-acetyl-5-methoxytryptamine

Method A



To a suspension,cooled on ice,of 20g (0.105 moles) of pure 5-methoxytryptamine in 400 ml methylene chloride there is slowly added,under stirring,a cold solution of 20 ml (0.21 moles) of acetic anhydride in 200 ml methylene chloride.Stirring and cooling are continued for 1 hour (the reaction progression can be controlled by TCL) so as to obtain a full solution;then the solution is washed with Na_2CO_3, 2 times,under prolonged stirring, and then with water.The organic phase,dried on Na_2SO_4 and evaporated,provides 24g (yield 98%) of lightly colored melatonin.

In order to obtain a white product it is sufficient to process,if necessary,by charcoal in acetone and then crystalize from acetone-water.There are obtained 20 g (yield 83%) with m.p 116-7 • C (Tottoli).

TLC on silica gel,chloroform-ethanol (9:1). Rf of about 0.60.

Yield 46.5%,calculated on 2-carboxyethyl-3-(2-phthalimidoethyl)-5-methoxy-indole.

Method B

To a suspension,cooled in ice,of 5g (26.3 moles) of raw 5-methoxytryptamine in 100 ml methylene chloride there is slowly added,under stirring,a cold solution of 5ml (52.6 moles) of acetic anhydride in 50 ml of methylene chloride.Stirring and cooling are continued for 1 hour (the reaction progression can be controlled by TLC),so as to obtain a complete solution;then the solution is washed by Na_2CO_3 2N x 2, under continuous stirring,and then by water.The organic phase, dried on anhydrous Na_2SO_4 and evaporated,provides 6g of raw melatonine,which is purified by chromatography on column (4cm;diameter/length ratio 1:5) of Merck silica gel (70-230 mesh) (120 g);the solution is eluted by methylene chloride in order to remove the scarcely polar products thereby providing pure melatonine by eluting with methylene chloride-acetone (8:2).There are obtained 4g of product (purifying yield 65%) which are crystalized from acetone-water. Melting point 116-7 • C (Tottoli).

TLC on silica gel,chloroform-ethanol (9:1), Rf of about 0.60.

Yield of 46% calculated from 2-carboxyethyl-3-(2-phtalimidoethyl)-5-methoxy-indole.

In order to better disclose the total synthesis method according to the present invention, reference is now made to the accompanying drawing,in which there is shown the diagram of the several steps of this method.

The thus obtained melatonin has such a purity that it can be used,in suitable packages,both in the tumoural prophylaxis and in the tumoural therapy,as well as against AIDS.

In fact it has been found that this product, administered in suitable doses and with suitable procedures,provides,in addition to the above mentioned effects, also specific effects,such as :

- auxiolytic and slightly hypnotic action (which is useful for improving the antipain effect) and an antispasm effect (which is indispensable in the therapy of primary tumours and brain metastases);
- a melotropic action,thereby it is possible to use comparatively high doses of radiation and chemical therapeutical substances;
- an antimitotic action,perhaps of the same type of those found on the microtubule arrangement and cilliar regeneration;
- a modulating action on the NK cell activity.

In this connection it should be pointed out that,in order to obtain the above mentioned effects, there are sufficient very small oral, I.M. or I.V. doses: from 2mg/day to 20 mg/day;higher doses should be avoided in order to prevent the antiaggregating action of melatonin on the circulating platelets.

In addition there has been recently found a possible relationship between opioid peptides and the action mode of melatonin.

This fact is very important,since opioid antagonists are able of slowing neoplastic growth,whereas opioid agonists seem to have an antimitotic action,both in vivo and in vitro.

In particular,melatonin has been found to be of essential importance in the following cases:

- neuroblastoms,glioblastoms and astrocytoms;
- leio and rabdomions;
- condro-osteo-mixo-liposarcomas;
- melanomas;
- tumours of the respiratory tract and lungs;
- tumours of the digestive tract;
- tumours of the reproductive tract, bladder and prostate;
- spino and basocellular epitheliomas;
- malignant lymphomas and,with a less efficacy in the Hodgkin lymphoma;
- plasmocytomas;
- thyroid tumours;
- mammary tumours;
- limphoblastic and cronic limphoid leukaemia
- mieloblastic and cronic mieloid leukaemia

Thus,we can reasonably think that the efficacy of melatonin in the above very different tumours is such as to advise its use because of its general indirect and not specific action,which,on the other hand, is very essential.

In this connection it should be moreover pointed out that in the last ten years,experimental reports have stressed the fact that the neuroendocrine system and immunity seem to be mutually related and that some diseases,characterized by immune disorders,may be due to alterations of this interrelationship.

Among the several modulating neuroendocrine factors effecting the immune system,pineal secretions and endogenous opioid peptides seem to have a very important function.

In fact it has been demonstrated that both, pineal gland and opioidergic system are involved in the control of cellular and tumoural growth.

At the immune system level,the endogenous opioid peptides seem to provide a stimulating action; in particular endorphins may,under given conditions, stimulate the NK activity and the interleukine production.

On the other hand,basic data seem to suggest that melatonin,i.e N-acetyl-5-methoxytryptamine has a very important function in maintaining an efficient immune response in rats,under induced immunitary experimental stimulation.

The effect provided by melatonin,under the disclosed experimental conditions,is hindered by the simultaneous administration of naltrexone;this suggests that the immunomodulating action of melatonin can by controlled by opioidergic mechanisms.

Under basal condition and in the absence of the stimulation of the immune system,in rats melatonin administration has no efficacy.

There has been moreover demonstrated that repeated administrations of pineal extracts induce lymphocytopoiesis and timic hyperplasia,whereas pinealhectomy causes thimic atrophy.

In this connection it should moreover be stressed that pineal endocrine function itself seems to be modulated by opioid tone and that,vice versa,some typical actions of opioid substances,such as analgesic action,are controlled by the activity of pineal gland and follow a circadian rhythm.

Thus,one may reasonably suppose that the pineal gland,through its main hormone melatonin as a structure involved into the modulation of the neuroendocrine activities,is able of controlling the effects exerted on the immunine system.

In fact, documented circadian variations of the NK activity could be related to the circadian rhythm of melatonin,as demonstrated by some recent results.

From a lot of experimental tests,it has been found that surprising results has been obtained in the treatment of patients affected by AIDS.

These patients have been treated with melatonin with doses of 20 mg per day and,after a long therapy, it has been demonstrated that they had a lower incidence of infections,with a significant increase of the " null cells",as determined by examination of peripheral blood.

Melatonin,or N-acetyl-5-methoxytryptamine, which has a formulation which constitutes the subject matter of the Italian Patent Application N° 23,323 A/79 in the name of the same Applicant,and which is herein included by reference,has been found to be able to provide significant improvements in the treatment of patients affected by AIDS.

The effect of melatonin is further incresed as melatonin is used together with azidotimidine.

In particular,patients effected by AIDS,who were treated with azidotimidine in a dose of 3mg/kg every four hours,and who required weekly blood transfusions because of alteration in the blood coagulation, and subjected to a simultaneous treatment with melatonin,in a dose of 20 mg per day, greatly reduced the collateral effects affording the possibility of performing blood transfusions at 8 week intervals.

Thus it has been found that melatonin is able to efficiently treat patients affected by AIDS, mainly in combination with other known treatment methods.

In this connection,it should be apparent that all of the details and the used doses can be suitably changed depending on each patient.

In particular,for a better use of melatonin, the present invention suggests to solubilize it with water in order to facilitate the therapeutical applications,by using a particular method.

In fact,as is known,melatonine is a substance scarcely soluble in water,and satisfactorily soluble at 40-45 • C.

After long experimentation Applicant has found that adenosine is adapted to easily dissolve melatonin in water.

In particular an optimal ratio has been found i.e:

- for a mole of melatonine (252.27g) must be used four moles of adenosine (267.26g).

From the above disclosure it should be apparent that the invention fully achieves the intended objects.

While the invention has been disclosed and illustrated with reference to some embodiments thereof, it should be apparent that the disclosed embodiments are susceptible to several modifications and variations all of which will come within the spirit and scope of the invention,as defined in the accompanying claims.

Claims

1. A total synthesis method for making N-acetyl-5-methoxy tryptamine having a high purity and being easily soluble in water for therapeutic use against acquired immunodeficiency syndromes,comprising the steps of combining potassium phthalimide and dibromopropane to provide 3-bromopropyl-phthalimide,adding acetacetic ester in the presence of anhydrous ethanol dissolved sodium to provide ethyl-2-acetyl-phthalimido-pentanoate and adding diazo-p-anisidine, to provide 2-carboxy-ethyl-3-(2-phthalimido-ethyl)-5-methoxy-indolecharacterized in that the tabs prepared 2- carboxy-ethyl-3-(2-phthalimiio-ethyl)-5-methoxy-indole is further processed by the further steps of mixing it with 2N NaOH to provide a mixture,refluxing said mixture at 135 • C for 2 1/2 hours to provide a full solution,holding stirring and temperature,adding a 20%(v/v) H_2SO_4 solution and further refluxing for four hours to provide raw 5-methoxytryptamine.

   The said raw 5-methoxytryptamine is refluxed for 12-14 hours with hexamethyl-disilazane,under refrigeration and sodium hydroxide protection distilling the solution under normal pressure so as to recover excess HMDS and distilling at a reduced pressure so as to provide a mixture of the mono- and bi-derivatives,hydrolizing the silyl derivative by aqueous methanol so as to provide 5-methoxytryptamine with a purification yield of 80%.

   The method further comprises the step of adding to an ice cooled suspension of said pure 5-methoxytryptamine, a cold solution of acetic anhydride in methylene chloride, cooling and stirring for one hour,so as to provide a full solution, and washing with 2N Na_2CO_3 twice and then with water, drying the organic phase on anhydrous Na_2SO_4 and evaporating so as to provide a slightly colored high purity N-acetyl-5-methoxy-tryptamine.

2. A method according to claim 1,characterized in that said method comprises the step of cooling in a refrigerator or a ice bath,said solution of 2-carboxyethyil-3-(2-phtalimidoethyl)-5-methoxy-indole with 2N NaOH and 20% (v/v) $H_2S\ O_4$ and removing by filtration the precipited phtalic acid.

3. A method according to claim 2,characterized in that said method comprises the further step of alkaly treating said cooled solution stripped from said precipited phtalic acid by 30% NaOH and extracting three times with CH_2Cl_2,washing with water the collected extracted materials, drying said collected extracted materials on anhydrous Na_2SO_4 and evaporating said materials so as to provide raw 5-methoxytyptamine.

4. A method according to claim 1 characterized in that said method comprises the further steps of processing with charcoal in acetone and then crystalizing said slightly colored N-acetyl-5-methoxy-

tryptamine from water-acetone so as to provide a white product.

5. A method according to claim 1,characterized in that said method further comprises the steps of adding to a suspension of raw 5-methoxytryptamine, methylene chloride,slowly stirring and further adding a cold solution of acetic anhydride in methylene chloride,continuously stirring and cooling so as to provide a full solution end washing with 2N Na_2CO_3 and then with water, drying on anhydrous Na_2SO_4 and evaporating the organic phase, so as to provide raw N-acetyl-5-methoxy-tryptamine by column cromatography.

6. A method for preparing a product according to claim 5 characterized in that said N-acetyl-5-methoxy tryptamine product is mixed with adenosine with a ratio of a mole of N-acetyl-5-methoxy-tryptamine for four moles of adenosine.

Patentansprüche

1. Ein Totalsyntheseverfahren zur Herstellung von N-Acetyl-5-methoxytryptamin hoher Reinheit und guter Wasserlöslichkeit zur therapeutischen Anwendung bei Syndromen erworbener Immunschwäche, umfassend die Schritte des Vereinigens des Kaliumsalzes des Phthalimids mit Dibrompropan, um 3-Brompropylphthalimid bereitzustellen, des Addierens von Acetessigester in Gegenwart von in absolutem Ethanol gelöstem Natrium, um Ethyl 2-Acetylphthalimidopentanoat bereitzustellen, und des Addierens von Diazo-p-anisidin, um 2-Carboxyethyl-3-(2-phthalimidoethyl)-5-methoxyindol bereitzustellen, dadurch gekennzeichnet
daß das so dargestellte Carboxyethyl-3-(2-phthalimidoethyl)-5-methoxyindolweiter mit den sukzessiven Schritten seines Vermischens mit 2N NaOH zum Bereitstellen eines Gemisches behandelt wird, des Erhitzens am Rückfluß bei 135° C für 1/2 Stunde, um vollständiges Auflösen zu bewirken, des Beibehaltens des Rührens und der Temperatur, des Hinzufügens von 20% (V/V) H_2SO_4 und des weiteren Erhitzens am Rückfluß über vier Stunden, um rohes 5-Methoxytryptamin bereitzustellen.
Das Verfahren umfaßt weiterhin den Schritt des Hinzufügens zu einer eisgekühlten Suspension dieses reinen 5-Methoxytryptamins einer kalten Lösung von Essigsäureanhydrid in Methylenchlorid, des Rührens und des Kühlens für eine Stunde zum Bewirken der vollständigen Auflösung, und des zweimaligen Waschens mit 2N Na_2CO_3 und dann mit Wasser, des Trocknens der organischen Phase auf wasserfreiem Na_2SO_4 und des Verdampfens davon, um so leicht gefärbtes N-Acetyl-5-methoxytryptamin hoher Reinheit bereitzustellen.

2. Ein Verfahren nach Anspruch 1, dadurch gekennzeichnet daß dieses Verfahren den Schritt des Kühlens mit einer Kühlmaschine oder einem Eisbad dieser Lösung von Carboxyethyl-3-(2-phthalimidoethyl)-5-methoxyindol, deren Behandlung mit 2N NaOH und 20% (V/V) H_2SO_4 und die Entfernung der abgeschiedenen Phthalsäure durch Filtration umfaßt.

3. Ein Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß dieses Verfahren den weiteren Schritt der alkalischen Behandlung dieser von dieser abgeschiedenen Phthalsäure befreiten, gekühlten Lösung mit 30%iger NaOH und das dreimalige Extrahieren mit CH_2Cl_2 umfaßt, des Waschens mit Wasser der vereinigten extrahierten Phasen, des Trocknens dieser vereinigten extrahierten Phasen mit wasserfreiem Na_2SO_4 und des Verdampfens dieser Stoffe, um so rohes 5-Methoxytryptamin bereitzustellen.
Dieses rohe 5-Methoxytryptamin wird 12-14 Stunden lang mit Hexamethyldisilazan am Rückfluß erhitzt, mit Kühlung und Schutz durch Natriumhydroxid, die Lösung bei atmosphärischem Druck zur Wiedergewinnung des überschüssigen HMDS destilliert und bei vermindertem Druck destilliert, um so ein Gemisch der mono- und bisubstituierten Derivate bereitzustellen; die Silylderivate werden mit wäßrigem Methanol hydrolysiert, um 5-Methoxytryptamin mit einer Reinigungsausbeute von 80% bereitzustellen.

4. Ein Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß dieses Verfahren den weiteren Schritt des Behandelns mit Aktivkohle in Aceton und des anschließenden Umkristallisierens dieses leicht gefärbten N-Acetyl-5-methoxytryptamins aus Wasser/Aceton umfaßt, um so ein weißes Produkt bereitzustellen.

5. Ein Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß dieses Verfahren weiterhin die Schritte des Hinzufügens einer Lösung von Essigsäureanhydrid in Methylenchlorid zu einer Suspension von rohem 5-Methoxytryptamin in Methylenchlorid bei leichtem Rühren umfaßt, des ständigen Rührens und

Kühlens, um eine vollständige Auflösung zu bewirken, und des Waschens mit 2N Na_2CO_3 und dann mit Wasser, des Trocknens auf wasserfrei m Na_2SO_4 und des Verdampfens der organischen Phase, um so rohes N-Acetyl-5-methoxytryptamin über Säulenchromatographie bereitzustellen.

6. Ein Verfahren zum Herstellen eines Produktes nach Anspruch 5, dadurch gekennzeichnet, daß dieses Produkt aus N-Acetyl-5-methoxytryptamin mit Adenosin in einem Verhältnis von einem Mol N-Acetyl-5-methoxytryptamin zu vier Mol Adenosin vermischt wird.

Revendications

1. Un procédé de synthèse totale pour produire la N-acétyl-5-méthoxytryptamine de grande pureté et facilement soluble dans l'eau pour l'utilisation thérapeutique contre les syndrômes d'immunodéficience acquise, comportant les étapes de l'ajoutage du sel potassique du phtalimide au dibromopropane afin de donner du 3-bromopropylphtalimide, de l'ajoutage d'ester acétylacétique en présence de sodium dissolu dans l'éthanol anyhdre afin de donner du 2-acétylphtalimidopentanoate d'éthyle, et de l'ajoutage de la diazo-p-anisidine afin de donner du 2-carboxyéthyl-3-(2-phtalimidoéthyl)-5-méthoxyindole, caractérisé en ce que le 2-carboxyéthyl-3-(2-phtalimidoéthyl)-5-méthoxyindole ainsi préparé est traité ultérieurement par les étapes successives de l'ajoutage du NaOH 2N afin de mettre en oeuvre un milieu réactionnel, du reflux dudit mélange à 135°C durant 1/2 heure afin de donner une dissolution complète en conservant l'agitation et la température, de l'ajoutage d'une solution 20% (v/v) de H_2SO_4 et du reflux successif durant quatre heures afin de donner de la 5-méthoxytryptamine brute.
Le procédé comprend en outre les étapes de l'ajoutage d'une suspension refroidie à la glace de ladite 5-méthoxytryptamine pure à une solution froide d'anhydride acétique dans le chlorure de méthylène, du refroidissement et de l'agitation durant une heure de manière à donner une dissolution complète, et de deux lavages par le Na_2CO_3 2N et puis par l'eau, du séchage de la phase organique sur le Na_2SO_4 anhydre et de l'évaporation, de manière à donner de la N-acétyl-5-méthoxytryptamine de grande pureté, faiblement colorée.

2. Un procédé selon la revendication 1, caractérisé en ce que ledit procédé comporte l'étape du refroidissement dans un réfrigérateur ou dans un bain à glace de ladite solution du 2-carboxyéthyl-3-(2-phtalimidoéthyl)-5-méthoxyindole, du traitement de ladite solution avec le NaOH 2N et le N_2SO_4 20% (v/v) et de l'élimination par filtration de l'acide phtalique précipité.

3. Un procédé selon la revendication 1, caractérisé en ce que ledit procédé comporte les étapes successives du traitement à l'alcali de ladite solution refroidie, libérée dudit acide phtalique précipité, par le NaOH 30% et de trois extractions au CH_2Cl_2, du lavage par l'eau des substances extraites réunies, du séchage desdites substances extraites réunies sur le Na_2SO_4 anhydre et de l'évaporation desdites substances pour donner de la 5-méthoxytryptamine brute.
Ladite 5-méthoxytryptamine brute est chauffée au reflux durant 12-14 heures avec le hexaméthyldisilazane, en réfrigérant et sous la protection de l'hydroxide de sodium, la solution est distillée sous pression normale afin de récupérer le HMDS en excès, puis distillée sous pression réduite de manière à donner une mixture des dérivatifs mono- et bifonctionnels, le dérivatif silylique est hydrolysé par le le méthanol aqueux pour donner de la 5-méthoxytryptamine avec un rendement de purification de 80%.

4. Un procédé selon la revendication 1, caractérisé en ce que ledit procédé comporte l'étape successive du traitement au charbon actif dans l'acétone et de la recristallisation de ladite 5-méthoxytryptamine faiblement colorée dans l'acétone aqueuse afin de donner un produit blanc.

5. Un procédé selon la revendication 1, caractérisé en ce que ledit procédé comporte les étapes successives de l'ajoutage, sous lente agitation, d'une solution refroidie d'anhydride acétique dans le chlorure de méthylène à une suspension de la 5-méthoxytryptamine brute dans le chlorure de méthylène, en maintenant l'agitation et le refroidissement jusqu'à obtenir une dissolution complète, et du lavage par le Na_2CO_3 2N et puis par l'eau, du séchage sur le Na_2SO_4 anhydre et de l'évaporation de la phase organique, de manière à donner de la N-acétyl-5-méthoxytryptamine par la chromatographie sur colonne.

6. Un procédé pour préparer un produit selon la revendication 5, caractérisé en ce que ledit produit constitué par la N-acétyl-5-méthoxytryptamine est ajouté à l'adénosine dans un rapport d'une mole de

N-acétyl-5-méthoxytryptamine pour quatre moles d'adénosine.